REMARKS

Claims 1-48 were pending. By this amendment, claims 3 and 36-48 are canceled without prejudice to their being pursued in the present application or in a related patent application. Therefore, claims 1-2 and 4-35 remain pending. Claim 1 is amended in view of art and to correct a minor error of form. Claims 13, 14, 15, 17, 27, 28, and 29 are amended for minor matters of form. The "Brief Description of the Figures" section of the specification is amended for matters of form. The other amendments to the specification are made solely to correct minor spelling errors. No new matter is entered by the amendment.

Drawings

Applicants thank the Examiner for the indication that the resubmitted Formal Drawings filed on April 11, 2002 were reviewed by the Draftsperson and approved.

Amendment to Claim 1

Applicants amend claim 1 to recite, among other things, administering stem cells to a subject. Applicants make this amendment in view of Strömberg et al, "Chronic implants of chromaffin tissue into the dopamine-denervated striatum. Effects of NGF on graft survival, fiber growth and rotational behavior." *Exp Brain Res* (1985) 60: 335-349. A copy of this paper is appended to the Reply for the Examiner's reference. Applicants note that their attention was drawn to this paper because it is referenced in Ip et al. (PCT WO 94/03199), which was cited by the Examiner as part of the rejection under 35 U.S.C. § 103(a).

Claim 1 as amended recites, among other things, administering stem cells to a subject. In contrast, Strömberg et al. does not teach administering stem cells to a subject. Rather, Strömberg et al. teaches grafting pieces of adrenal medulla. Strömberg et al. is silent as to whether the pieces of adrenal medulla include stem cells. Therefore, claim 1 as amended is not anticipated by Strömberg et al.

Objections to Claims

The Examiner objected to claims 13, 14, 38, 39, 42, 43, and 48 for reciting "SEQ. ID. Nos." instead of --SEQ ID Nos--. Claims 38, 39, 42, 43, and 48 are canceled, rendering moot the objection to these claims. Claims 13 and 14, as well as claims 27 and 28 have been amended solely to correct the minor error of form identified by the Examiner. Applicants respectfully request reconsideration and withdrawal of the objection to these claims.

Objections to Specification

The Examiner objected to the disclosure because the "Brief Description of the Figures" section makes reference to both Figure 1 and Figure 1A, and to both Figure 2 and Figure 2A. In response, Applicants amend the specification to delete the paragraphs in the Brief Description of the Figures that refer to Figure 1 and to Figure 2. Applicants respectfully request reconsideration and withdrawal of the objection to the specification.

Claims are Enabled under 35 U.S.C. § 112, first paragraph

Claims 1-48 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that the "specification... does not reasonably provide enablement for a method of treating a subject with CNS damage... [or] for the use of the method of the invention in treating the

various diseases claimed." (Office Action dated 6/19/02, page 3). Applicants respectfully traverse the rejection as to claims 1-2 and 4-35, the cancellation of claims 3 and 36-48 having rendered moot the rejection of those claims.

Amount of direction provided and existence of working examples:

The Examiner asserted that the specification "fails to disclose how long the enhanced recovery in rats lasts, and whether it is long enough to see a therapeutic effect," and also that the working examples provided in the specification "do not provide sufficient guidance on how to determine the appropriate dosage and other parameter such as the best route of administration, and frequency of administration." (Office Action dated 6/19/02, page 5).

Applicants respectfully disagree. First, Applicants contend that length of recovery is irrelevant to the sufficiency of an enabling description. Rather, Applicants note that the enablement analysis concerns whether the disclosure enables a person of ordinary skill in the art to practice the claimed subject matter, not how well the claimed subject matter works. Second, Applicants refer the Examiner to pages 33-34 and Table 2 of the specification for description of dosages, to page 33 for description of routes of administration, and to page 34 for description of dosage frequency. Applicants submit that these passages describe these parameters in sufficient detail to enable one of ordinary skill in the art to practice the claimed subject matter.

As to dosage, the Examiner asserted that "it would be difficult to predict the brain weight of a human being" (Office Action dated 6/19/02, page 8), yet the Examiner points to no teaching in the art of record to support this assertion. The specification discloses

exemplary dimensions of the human brain (see page 33, lines 20 and 22) and thereby provides enabling data for predicting and/or determining the appropriate dose.

Applicants further submit that they need not identify which route of administration is best; rather, the best mode of administration contemplated merely must be disclosed. *See* M.P.E.P § 2165.01, subsection III ("There is no requirement in the statute that applicants point out which of their embodiments they consider to be their best; that the disclosure includes the best mode contemplated by applicants is enough to satisfy the statute.")

Predictability and amount of experimentation

The Examiner asserted that the disclosure in the specification "does not predict success in humans." (Office Action dated 6/19/02, page 11). Applicants contend that predictability of success in humans is irrelevant to the enablement analysis. Rather, the prediction of the applicability of one teaching to another is the relevant test. The specification provides detailed, quantitative teachings as to dosage in rats (see pages 33-34, 41-42, 44, and Table 2). The specification further provides detailed, quantitative scaling data for adjusting the dose to humans (see page 33 and Table 2). Because the specification expressly teaches how to adjust the dosage from the rat to the human, Applicants submit that the specification need not rely on the inherent predictability of the general field of endeavor of the claimed subject matter.

Finally, the Examiner asserted that the use of "a rat model of stroke recovery... is not an appropriate model for all the diseases covered by the claims." (Office Action dated 6/19/02, page 12). Applicants respectfully disagree. First, Applicants point out that claims

1-2 and 4-35 do not recite treatments of particular diseases. Rather, the diseases recited in the claims are associated with CNS damage and/or brain damage, and the claims are directed to methods of treating a subject with CNS damage (claim 1) or with brain damage (claim 17). Therefore, at issue in the enablement analysis is whether the specification adequately teaches a method of treating a subject with CNS damage or with brain damage, not whether the specification teaches how to treat a particular disease. Furthermore, the specification teaches that a wide variety of CNS and/or brain disorders can be treated using the disclosed methods (see page 12, paragraph beginning line 18). Indeed, the literature cited by the Examiner emphasizes that similar approaches are often taken to treat CNS or brain damage, whatever its cause. For example, Park et al. describes that neural stem cell transplantation is being studied to treat a wide variety of CNS degenerative disorders.

For at least the reasons given above, Applicants contend that claims 1-2 and 4-35 are adequately enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-2 and 4-35 under 35 U.S.C. 112, first paragraph for lack of enablement.

Claims are Supported under 35 U.S.C. § 112, first paragraph

Claims 13, 27, 38, 42, and 48 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserted that "the specification fails to describe a representative number of the sequences encompassed by the said genus..." (Office Action dated 6/19/2002, page

13). Applicants respectfully traverse the rejection as to claims 13 and 27, the cancellation of claims 38, 42, and 48 having rendered moot the rejection of those claims.

Applicants refer the Examiner to page 14, lines 18-26 of the specification as filed, among other places, wherein no fewer than 9 factors being at least 30% identical to one of the disclosed sequences are disclosed and their general tertiary structure described. The specification makes further reference to other members of the FGF family, also being at least 30% identical to one of the disclosed sequences. The specification also provides citations to the papers of Stauber et al.,Wong et al., and Szebenyi et al., in which various members of this family are described. Applicants therefore submit that the disclosure provides adequate evidence that this family of sequences and their relatedness was known in the art at the time the application was filed. On this basis, Applicants contend that a sufficient number of species of the claimed genus are disclosed to support the claimed genus, and that the species are identified with sufficient identifying characteristics to convey to one of ordinary skill in the art the inventors had possession of the claimed subject matter at the time the application was filed.

Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 13 and 27 under 35 U.S.C. § 112, first paragraph for lack of written description.

Claims are Definite under 35 U.S.C. § 112, second paragraph

Claim 14 was rejected as indefinite under 35 U.S.C. § 112, second paragraph because it recited in part "polypeptide show in one of". In response, Applicants amend

claim 14 to recite --polypeptide shown in one of--. This amendment is made solely to correct this minor typographical error and not for reasons of patentability.

Claims 15 and 29 were rejected as indefinite under 35 U.S.C. § 112, second paragraph on the ground that the phrase "selected from the following group:" is improper Markush language. In response, Applicants amend claims 15 and 29 to recite "selected from the group consisting of:" Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 14, 15, and 29 under 35 U.S.C. § 112, second paragraph.

Claim rejections under 35 U.S.C. § 102

Claims 41-43 were rejected under 35 U.S.C. § 102(a) as anticipated by Rosen et al, WO 00/71715.

Claims 36-43 were rejected under 35 U.S.C. § 102(b) as anticipated by Flax et al. (*Nat. Biotechnol.* 16:1033).

Claims 44-48 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent 5,968,829 to Carpenter, issued October 19, 1999.

Claims 41-43 were rejected under 35 U.S.C. § 102(b) as anticipated by FR 2 642 086, inventors Caput et al.

Claims 41-42 were rejected under 35 U.S.C. § 102(b) as anticipated by EP 0 226 181, inventors Moscatelli et al.

Claims 41-43 were rejected under 35 U.S.C. § 102(a) as anticipated by EP 0 326 907, inventors Senoo et al.

In response, Applicants note that claims 36-48 have been canceled, rendering moot the above-listed rejections. The cancellation of these claims is made solely to expedite prosecution and is not an acquiescence to the rejections or an admission as to the merits of the rejections. Applicants reserve the right to pursue the canceled claims and additional claims in subsequent applications. Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102.

Claim rejections under 35 U.S.C. § 103(a)

Claims 1-35 were rejected under 35 U.S.C. § 103(a) as "unpatentable over Andsberg et al. (1998; European Journal of Neuroscience vol. 10. no.6, pp.2026-2036), Alp. et al. (U.S. Patent S No. 5,733,871) further in view of Ip et al. (1994; PCT International Publication Number WO 94/03199) and Daughaday et al. (1989, Endocr. Rev. 10:68-91)." (Office Action, June 19, 2002, page 24). The Examiner stated that "it would have been obvious to one of ordinary skill in the art to be motivated to use the combination approach of using the stem cells and the bFGF together in a method for preventing cell death or stimulating the growth of new neurons, with a reasonable expectation of success. The motivation to do so and the expectation of success was provided by the teachings of Ip et al. (1994) who successfully demonstrated the synergistic effect of using a combination approach in increasing the effectiveness of the neural stem cells." (Office Action, June 19, 2002, page 25).

In response, Applicants respectfully traverse this rejection. Applicants respectfully disagree with the Examiner's characterization of Ip. First, Applicants note that the Examiner did not point out where in Ip any "synergistic effect of using a combination

approach in increasing the effectiveness of the neural stem cells" is "successfully demonstrated." Applicants point out that "the particular part [of a reference] relied on must be designated as nearly as practicable." 37 C.F.R. § 1.104(c)(2); M.P.E.P. § 707.

More significantly, however, Applicants can find no teaching in Ip of a method of administering to a subject stem cells and a neural stimulant wherein the conjoint administration of the stem cells and the neural stimulant ameliorates the effects of CNS damage. At best, Ip makes an unsupported speculation of "co-injection of NGF... with CNTF/bFGF pretreated cells." (Ip, page 15, line 27 to page 16, line 2). Ip provides no data to support this speculation. Rather, the examples provided describe only culture conditions and in vitro assays, not administration. Furthermore, Ip does not describe how to perform the injection, routes of administration, the amounts of the components to inject, the dosage frequency, or other supporting disclosure that would enable one of ordinary skill in the art to perform the speculated method, or that would convey to one of ordinary skill that the inventors possessed their speculated method.

Therefore, Ip provides no enabling disclosure for conjoint administration of stem cells and a neural stimulant. The Examiner acknowledges that the other references similarly fail to teach conjoint administration of stem cells and a neural stimulant. Therefore, Applicants submit that even if Andsberg, Alps, and Daughaday were combined with Ip, the combination still would not teach or suggest conjoint administration of stem cells and a neural stimulant. Moreover, Ip provides no motivation to combine the other references, because Ip, in lacking an enabling description of co-injection, does not teach or suggest how the other references might be combined.

With specific reference to claims 4, 5, 20, and 21, Applicants further note that Ip provides no teaching or suggestion of conjoint administration of a neural stimulant with neural stem cells or hematopoietic stem cells. Ip provides to teaching or suggestion that the CNTF/bFGF pretreated cells are stem cells, neural stem cells, or hematopoieitc stem cells.

For at least the reasons given above, Applicants contend that independent claims 1 and 17 are not obvious in light of the cited references, taken either singly or together. Claims 2, 4-16 and 18-35 depend variously and ultimately from claims 1 and 17. As such, these dependent claims must be read to include the elements set forth in their respective independent claims and in any other intermediate claims from which they depend. Therefore, the dependent claims are also not obvious in light of the cited references. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-2 and 4-35 under 35 U.S.C. § 103(a).

CONCLUSION

In light of the above, the claims of the above-referenced application are allowable. Applicants therefore respectfully request allowance of all pending claims so that this case can pass to issue.

No fees are believed due in connection with the filing of this Reply, except for the fee accompanying the Petition for a Three Month Extension of Time. However, the Commissioner is hereby authorized to charge or credit to our Deposit Account, No. **06-1448**, any fees due or overpayment thereof, respectively, in connection with the filing of this Reply.

If any questions remain, Applicants invite the Examiner contact the undersigned at (617) 832-1176 or at the phone number below.

Respectfully submitted,
FOLEY HOAG LLP

Dated: December 19, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please replace the paragraph beginning at page 10, line 7 with the following paragraph:

--"Neuroepithelial stem cells" are stem cell populations isolated from fetal neuroepithelial tissue. Such cells may be considered a subset of neural stem cells, as used herein. "Neuroepithelial ~~Neuroeptihelial~~ cells" tend to be multipotent.--

Please replace the paragraph beginning at page 12, line 18 with the following paragraph:

--The subject method has wide applicability to the treatment of CNS damage. In this regard, the subject method is useful for, but not limited to, treatment of injury to the brain and spinal cord due to ischemias, hypoxia, traumas, neurodegenerative diseases, infectious diseases, cancers, autoimmune diseases and metabolic disorders. Examples of disorders include stroke, head trauma, spinal trauma, hypotension, arrested breathing, cardiac arrest, ~~Rey's~~ Reye's syndrome, cerebral thrombosis, embolism, cerebral hemorrhage, brain tumors, encephalomyelitis, hydroencephalitis, operative and postoperative brain injury, Alzheimer's disease, Huntington's disease, Creutzfeld-Jakob disease, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis.--

Please replace the paragraph beginning at page 21, line 22 with the following paragraph:

--Each of these analogs can subsequently be screened for further biological activities. For example, receptor-binding analogs isolated from the combinatorial library can be tested for their effect on cellular proliferation relative to the wild-type form of the protein. Alternatively, one could screen the analogs for stability in vitro or in vivo. The activity of such analogs can also be assessed in animal models. For example, the ability of an analog to improve neural function in a ~~a~~ rat stroke model could be assessed to verify that an analog has the appropriate bioactivity.--

Please replace the paragraph beginning at page 22, line 15 with the following paragraph:

--In other embodiments, chemically modified bioactive factors are contemplated. A polypeptide may be chemically modified to create derivatives by forming covalent or ~~aggregrative~~ aggregative conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like. Covalent derivatives may be prepared by linking the chemical moieties to functional groups on amino acid side chains or at the N-terminus or at the C-terminus of the polypeptide. For instance, a bioactive factor can be generated which includes a moiety, other than sequences naturally associated with the protein, that binds a component of the extracellular matrix and enhances localization of the analog to cell surfaces. For example, sequences derived from the fibronectin "type-III repeat", such as a tetrapeptide sequence R-G-D-S (Pierschbacher et al. (1984) *Nature* 309:30-3; and Kornblihtt et al. (1985) *EMBO* 4:1755-9) can be added to a polypeptide factor to support attachment of the chimeric molecule to a cell through binding ECM components (Ruoslahti et al. (1987) *Science* 238:491-497; Pierschbacheret al. (1987) *J.*

Biol. Chem. 262:17294-8.; Hynes (1987) *Cell* 48:549-54; and Hynes (1992) *Cell* 69:11-25).--

Please replace the paragraph beginning at page 37, line 27 with the following paragraph:

--Particular compositions for use in the method of the present invention are those wherein the neural stimulant is formulated in liposome-containing compositions. Liposomes are artificial vesicles formed by amphiphatic molecules such as polar lipids, for example, phosphatidyl cholines, ethanolamines and serines, sphingomyelins, cardiolipins, plasmalogens, phosphatidic acids and ~~cerebiosides~~cerebrosides. Liposomes are formed when suitable ~~amphiphathic~~ amphipathic molecules are allowed to swell in water or aqueous solutions to form liquid crystals usually of multilayer structure comprised of many bilayers separated from each other by aqueous material (also referred to as coarse liposomes). Another type of liposome known to be consisting of a single bilayer encapsulating aqueous material is referred to as a unilamellar vesicle. If water-soluble materials are included in the aqueous phase during the swelling of the lipids they become entrapped in the aqueous layer between the lipid bilayers.--

Please replace the paragraph beginning at page 39, line 15 with the following paragraph:

--The organic component consists of a suitable non-toxic, pharmaceutically acceptable solvent such as, for example ethanol, glycerol, propylene glycol and polyethylene glycol, and a suitable phospholipid which is soluble in the solvent. Suitable

phospholipids which can be employed include lecithin, phosphatidylcholine, ~~phosphatydylserine~~phosphatidylserine, phosphatidylethanol-amine, phosphatidylinositol, lysophosphatidylcholine and ~~phospha-tidyl-~~phosphatidyl glycerol, for example. Other lipophilic additives may be employed in order to selectively modify the characteristics of the liposomes. Examples of such other additives include stearylamine, phosphatidic acid, tocopherol, cholesterol and lanolin extracts.--

Please replace the paragraph beginning at page 42, line 24 with the following paragraph:

--The results of these tests are shown in ~~Figure 1~~Figures 1A-1D. Panels (A) and (B) show placing activity of the affected forelimb and hindlimb (contralateral to the side of the stroke in the brain). Panel (C) shows the body swing test, and panel (D) shows the spontaneous limb use test. In each instance, normal behavior is indicated by the data obtained on the day before surgery (-1 day). In each case, animals showed markedly abnormal behavior on the day following surgery. There was then a slow spontaneous recovery that was incomplete. ~~Figure 1 shows~~ Figures 1A-1D show that on the limb placing tests all three treatments: NSC, bFGF and the combination, significantly enhanced recovery compared to placebo. There was a similar trend in the spontaneous limb use test. No differences among treatments compared to placebo were seen on the body swing test. In addition, although this was nonsignificant, a trend toward superior enhancement of function was seen in the combination group compared to the NSC and bFGF groups alone.--

Please replace the paragraph beginning at page 44, line 28 with the following paragraph:

--The results of these behavioral tests are shown in Figures ~~2~~ 2A-2D and 3. Again, all three treated groups: NSC, bFGF, and the combination of NSC + bFGF, showed superiority in recovery on the forelimb and hindlimb placing tests compared to placebo. Again, there was a trend towards best recovery in the combination group. In the body swing test, NSC treatment alone did not show advantage over placebo, but both the bFGF and combination groups did. In the spontaneous limb use test, only the combination group showed a trend toward improved outcome. Finally, in the paw reaching test, the combination group appeared to show superiority compared to either treatment alone. Histological evaluation of these brains is still pending.--

In the claims:

Claims 1, 13, 14, 15, 17, 27, 28, and 29 are amended as follows:

1. (AMENDED) A method of treating a subject with CNS damage, said method comprising administering to said ~~patient~~subject:

    - stem cells; and

    - a neural stimulant

    wherein the conjoint administration of cells and neural stimulant ameliorates the effects of CNS damage.

13. (AMENDED) A method of claim 9 wherein said polypeptide growth factor is a polypeptide at least 30% identical to a bFGF polypeptide shown in one of ~~SEQ. ID. Nos.~~SEQ ID Nos 1-3.

14. (AMENDED) A method of claim 12 wherein said polypeptide is identical to a bFGF polypeptide ~~show~~ shown in one of ~~SEQ. ID. Nos.~~SEQ ID Nos 1-3.

15. (AMENDED) A method of claim 1 wherein said neural stimulant is selected from the ~~following~~ group consisting of: a neurotransmitter, a neurotransmitter agonist, a neurotransmitter antagonist, a differentiation factor, a guidance molecule and transcranial magnetic stimulation.

17. (AMENDED) A method of treating a subject with brain damage resulting from stroke, said method comprising administering to said ~~patient~~subject:

- stem cells; and

- a neural stimulant

wherein the conjoint treatment with cells and neural stimulant ameliorates the effects of brain damage.

27. (AMENDED) A method of claim 23 wherein said polypeptide growth factor is a polypeptide at least 30% identical to a bFGF polypeptide shown in one of ~~SEQ. ID. Nos.~~SEQ ID Nos 1-3.

28. (AMENDED) A method of claim 23 wherein said polypeptide is identical to a bFGF polypeptide shown in one of ~~SEQ. ID. Nos.~~SEQ ID Nos 1-3.

29. (AMENDED) A method of claim 17 wherein said neural stimulant is selected from the ~~following~~ group consisting of: a neurotransmitter agonist, a neurotransmitter antagonist, a differentiation factor, a guidance molecule and transcranial magnetic stimulation.